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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/407,430	Applicant(s) WORMAN ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-56* is/are pending in the application.

4a) Of the above claim(s) *50-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on 10/09/02 in Paper No. 20 has been entered.

Amended claims 44-49 and newly added claims 50-56 are pending in the present application.

Newly submitted claims 50-56 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Firstly, new claims 50-55, drawn to a method of modifying the activity of the hepatitis C virus envelope E2 protein, which comprises contacting the E2 protein with an E_0 protein having amino acids 1-120 of SEQ ID NO:1, has different method steps (e.g., contacting the E2 protein with the E_0 protein rather than contacting the cell with an effective amount of the E_0 protein in a subject), different desired end-results (modifying the activity of hepatitis C virus envelope E2 protein vs inhibiting attachment of hepatitis C virus onto a cell in subject), and therefore it requires different technical considerations for attaining the desired end-results from the method of inhibiting attachment of hepatitis C virus onto a cell in a subject as recited in the amended claims 44-49 which are drawn to the originally presented invention.

Secondly, new claim 56, drawn to an isolated complex between the hepatitis C virus envelope E2 protein and an E_0 protein having amino acids 1-120 of SEQ ID NO:1 is not required in any manner for the practice of the method of inhibiting attachment of hepatitis C virus onto a cell in a subject as recited in the amended claims 44-49 which are directed to the originally presented invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 50-56 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Amended claims 44-49 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

Amended claims 44-49 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Amended claims 44-49 are drawn to a method of inhibiting attachment of hepatitis C virus onto a cell, which comprises contacting the cell with an effective amount of an E_0 protein having amino acids 1-120 of SEQ ID NO:1 to the subject, wherein the E_0 protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein; the same method with various limitation in the dependent claims.

The specification teaches by exemplification that using the yeast two hybrid assay, two clones encoding a portion of a protein were selected from a library of human liver Matchmaker cDNA for interacting with a portion of hepatitis C virus E2 lacking its most hydrophobic, carboxyl terminal domain. The sequence of the encoded portion of a protein, referred to as E_o protein, has the amino acid sequence of SEQ ID NO: 1. Furthermore, the specification teaches that the encoded amino acid sequence containing amino acid residues 1-120 of SEQ ID NO:1 (or E_o1 protein) is also capable of binding to the portion of hepatitis C virus E2 as does the E_o protein of SEQ ID NO:1, although at a relatively weaker binding affinity (See specification, pages 18-20).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention which is drawn to a method of inhibiting attachment of hepatitis C virus onto a cell in a subject using an effective amount of E_o protein having amino acids 1-120 of SEQ ID NO:1.

When read in light of the specification, the sole purpose for the claimed method is to attain therapeutic effects against hepatitis C infection in a subject through the use of an effective amount of an E_o protein having amino acids 1-120 of SEQ ID NO:1 to

inhibit the attachment of hepatitis C virus onto a cell. The instant specification is not enabled for the claimed invention because it fails to provide any guidance regarding the use of any effective amount of an E_o protein having amino acids 1-120 of SEQ ID NO:1 to treat or prevent hepatitis C infection in any subject or to prevent the attachment of hepatitis C virus onto a cell in a subject. The specification fails to teach or demonstrate a correlation or a nexus between the binding interaction of the E_o protein having SEQ ID NO:1 and the E_o1 proteins with a portion of the hepatitis C virus E2 envelope protein observed via the yeast two hybrid assay with any of the therapeutic effects contemplated by the claimed invention which comprise the inhibition of HCV replication, stopping or delaying the progression of liver disease in a subject or to prevent attachment of hepatitis C virus onto a cell in a subject. Apart from the yeast two hybrid assay system, there is no evidence of record indicating or suggesting that a similar interaction between E_o or E_o1 protein with a portion of the hepatitis C virus E2 envelope protein would also occur in other non-yeast biological systems, let alone for attaining the desired results contemplated by Applicants. Rosa et al. (Proc. Natl. Acad. Sci. 93:1759-1763, 1996; IDS) have reported that in contrast to E2 protein expressed in mammalian cells, E2 protein expressed in yeast or insect cells are not capable of binding to human cells (see Fig. 1), nor do they elicit neutralizing antibodies to protect chimpanzees from primary infection by an homologous hepatitis C isolate (page 1761, col. 2, top of first full paragraph). Thus, it is unclear about the significance of the interaction between E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein solely in yeasts as reported in this application to the desired results contemplated by Applicants to be

attained in a subject. Furthermore, in a review on the yeast two-hybrid system (Current Opinion in Biotechnology 6:59-64, 1995), Luban et al. have noted that a major problem associated with two-hybrid screens is the appearance of false-positives inherent in any transcriptional readout, and strong evidence for a direct interaction between the proteins should be provided in a biochemical assay, preferably one should show that the two proteins co-precipitate in their native context (page 62, col. 1, second full paragraph). Luban et al. further stated "The last issue, which is usually the most difficult aspect of working with the two hybrid system, is that one must demonstrate the functional significance of the protein-protein interaction that one has discovered" (page 62, col. 1, top of the third full paragraph). Since the prior art at the filing date of the present application does not provide any guidance regarding to the use of any effective amount of E_o or E_o1 protein to attain the results contemplated by Applicants in a subject, it is incumbent upon the instant specification to do so. Particularly, at the filing date of the present application, standard treatments for patients infected with hepatitis C include therapies using recombinant alpha interferon alone or in combination with the nucleoside analogue Ribavirin, whose actions are not mediated via inhibiting the attachment of hepatitis C virus onto cells (Gish, Seminars in liver disease 19 (S1): 35-47, 1999; Cited previously). Since the physiological art is recognized as unpredictable (MPEP 2164.03), and as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle

factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, with the lack of guidance provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

At the filing date of the present application, it was already known in the art that other polypeptides such as the CD81 protein (Abrignani et al., WO 99/18198; see page 2, lines 18-25; Cited previously), annexin V, tubulin, apolipoprotein B (Maertens et al., WO 99/24054; see abstract; Cited previously), as well as endogenous host proteins such as the chaperone protein calnexin and lactoferrin are also capable of binding at least to the hepatitis C virus envelope protein E2 (Maertens et al., WO 99/24054; page 2, lines 12-29). However, the potential therapeutic values of these proteins for treating HCV infection in a subject remain to be determined or investigated because the mechanism by which HCV enters target cells remains unknown (Flint et al., J. Virol. 73:6782-67900, 1999; page 6782, column 2, last three lines). Flint et al. stated that "Clearly, it will be important to demonstrate whether CD81, either alone or with additional factors, can function as the HCV receptor in allowing pseudotyped virus-cell attachment and entry. Since CD81 is so widely expressed, it is unlikely to be the sole factor determining HCV liver tropism" (page 6789, column 1 lines 1-6). Since it is unclear how hepatitis C virus enters target cells in the art at the filing date of the present application, then how the simple binding of E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein in a yeast two-hybrid assay can be reasonably extrapolated to inhibiting attachment of HCV virus onto any cell in a subject as claimed to attain

therapeutic effects contemplated by Applicants. Additionally, even suppose that the simple binding of any protein with the E2 envelope protein is a reasonable correlation for preventing attachment of HCV virus onto cells in a subject, and thereby treating or preventing HCV infection, then why CD81, annexin V, tubulin, apolipoprotein B as well as calnexin and lactoferrin have not been routinely used in the treatment or therapy for patients infected with HCV? With the absence of sufficient guidance provided by the instant specification, particularly with the lack of any *in vivo* example (part of guidance), it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

With respect to the use of an E_o protein having amino acids 1-120 of SEQ ID NO: 1 in the method as claimed, it is unclear whether the E_o protein is capable of exhibiting an effective binding affinity for the full-length E2 envelope protein presented on the surface of the hepatitis C virus, usually in complexes with other viral envelope components, such as the E1 envelope protein, such that it can disrupt such complexes and thereby preventing the attachment of hepatitis C virus onto any cell or preventing or treating hepatitis C virus infection in a subject. Gish noted that the standard management of chronic HCV infection is complicated by various factors, including: the rapid mutation rate of the HCV genome, particularly the hypervariable region, the lack of neutralizing antibodies to HCV gene products, and the lack of sequence homology (less than 72%) among various subtypes of HCV (page 36, column 1, first full paragraph, line 8 continues to the first paragraph on column 2). It is also thought that the binding of E2 to target cells mostly involves the highly variable amino terminus of E2, the

hypervariable region I (Maertens et al., WO 99/24054; page 2, lines 12-17). As such, it is unclear whether E_o or E_o1 protein, is capable of binding efficiently *in vivo* to the highly variable region of E2 in any HCV subtype such that it can inhibit the attachment of HCV onto any cell and thereby treating and preventing HCV infection in a subject. Therefore, given the complete lack of guidance provided by the instant specification regarding to the effective *in vivo* use for any E_o protein that is capable of inhibiting the attachment of hepatitis C virus onto cell so as to treat and prevent HCV infection in a subject, it would have required undue experimentation for a skilled artisan to make and use the claimed invention.

The instant claims encompass any route of administering the E_o protein into a subject to inhibit attachment of hepatitis C virus onto a cell in a subject. However, the instant specification fails to provide any relevant information regarding to the *in vivo* stability of the E_o protein utilized or how to overcome random degradation of the administered E_o protein in a treated host and more importantly how to target the E_o protein to a desired tissue or organ in an effective amount by any means of delivery such that any therapeutic effects (treatment and prevention) or preventing attachment of hepatitis C virus onto any cell in a subject as contemplated by Applicants could be attained. Again, in the absence of any guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the state of the art on treatment of hepatitis C at the

effective filing date of the present application, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 10/09/02 in Paper No. 20 (pages 6-8) have been fully considered.

With respect to the doubt on the significance of the interaction between E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein in a yeast hybrid assay observed in the present application due to the inability of E2 protein expressed in yeast or insect cells to bind to human cells (see Fig. 1), and to elicit neutralizing antibodies to protect chimpanzees from primary infection by an homologous hepatitis C isolate in contrast to mammalian expressed E2 protein (page 1761, col. 2, top of first full paragraph) as taught by Rosa et al. (Proc. Natl. Acad. Sci. 93:1759-1763, 1996; IDS), Applicants argue that Rosa et al. performed methods having different steps in expressing their mammalian, yeast and insect E2 proteins, and the differences in the method steps contribute to the modification of the E2 proteins expressed in mammalian and yeast or insect cells that result in the differences observed in their binding to human cells and eliciting neutralizing antibodies against E2 proteins. Additionally, Applicants argue that Rosa et al. expressed the full-length sequence of E2 which included the transmembrane, which includes an endoplasmic reticulum retention signal, and yet the molecule is secreted, therefore Rosa et al. must have done something which also

modified the E2 binding activity in the yeast system. Applicants also argue that Cocquerel et al. (J. Virol. 72:2183-2191, 1998; Exhibit 1) confirm that "only a shorter secreted form of E2 glycoprotein ending at amino acid 661 appears to be properly folded" (page 2183, right column, lines 4-6 of the Cocquerel's article. Applicants further argue that based on the observation that complex-glycosylated secreted fraction of E2 expressed even in mammalian cells do not bind to human cells reported by Heile et al. (J. Virol. 74:6885-6892, 2000; Exhibit 2), it is likely that the different purification used by Rosa et al. between the mammalian expressed E2 and the yeast expressed E2 resulted in differences in glycosylation of their E2, and assert that Applicants' truncated E2 protein expressed in the two yeast two hybrid assay is more closely resemble to the E2 protein on HCV. Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, Rosa et al. clearly state "The finding that HCV-E2 binds with high affinity to target cells only when expressed in mammalian cells is most likely to the "physiologic" N-glycosylation and conformation it undergoes when expressed in mammalian cells" (page 1762, col. 1, first paragraph of the Discussion section), indicating that the authors do not think that the differences in the method steps for expressing and purification of mammalian, insect and yeast E2 proteins contribute to their differences in binding to target cells. It is noted that the same $E2_{384-715}$ protein is expressed in CHO cells, insect and yeast cells.

Secondly, the $E2_{384-715}$ protein expressed in CHO cells, insect and yeast cells would be expected to be secreted because Cocquerel et al. also state "The E2

glycoprotein extends to residue 746 (position on the polyprotein), and deletion of at least 31 C-terminal amino acids lead to its secretion" (page 2183, last line in col. 1 continues to line 2 of col. 2). Therefore, Rosa et al. did not have to do something that modify the E2 binding activity in the yeast system in order to make the $E2_{384-715}$ protein to be secreted as asserted by Applicants.

Thirdly, although Cockerel et al. state "However, only a shorter secreted form of E2 glycoprotein ending at amino acid 661 appears to be properly folded (32)" (page 2183, col. 2, lines 4-6 in the first paragraph) in the introduction section, Cockerel et al. do not confirm the statement in anyway with any factual evidence. Moreover, if the $E2_{384-715}$ protein is not properly folded, then why mammalian expressed $E2_{384-715}$ protein is still able to bind to target cells and induces neutralizing antibodies specifically against E2 protein in chimpanzees? And why is the $E2_{384-715}$ protein selectively folded properly only in mammalian cells and not insects and yeast cells?

Fourthly, Applicants fail to provide any objective evidence showing which purification step used by Rosa et al. resulted in the differences in glycosylation of mammalian and yeast expressed E2 proteins that contribute to the differences observed in their binding capability to target cells. Examiner is not aware of any isolation step that would result or cause complex-glycosylation for a secreted protein during the purification procedure, particularly in the method used by Rosa et al. Particularly, Rosa et al. clearly state "The finding that HCV-E2 binds with high affinity to target cells only when expressed in mammalian cells is most likely to the "physiologic" N-glycosylation

and conformation it undergoes when expressed in mammalian cells" (page 1762, col. 1, first paragraph of the Discussion section),

Finally, Applicants' truncated $E2_{384-661}$ expressed in the yeast two hybrid assay system is not a physiological form of E2 protein that would be present on the surface of HCV, because Applicants' truncated E2 protein is fused with the GAL4 DNA binding domain, and that it is not even at least in the non-covalent E1-E2 complex, a functional unit that mediates entry of HCV into target cells (Yi et al., Virology 231:119-129, 1997; Cited by Applicants previously in Exhibit 17). Moreover, in a review on the yeast two-hybrid system (Current Opinion in Biotechnology 6:59-64, 1995), Luban et al. have noted that a major problem associated with two-hybrid screens is the appearance of false-positives inherent in any transcriptional readout, and strong evidence for a direct interaction between the proteins should be provided in a biochemical assay, preferably one should show that the two proteins co-precipitate in their native context (page 62, col. 1, second full paragraph). Luban et al. further stated "The last issue, which is usually the most difficult aspect of working with the two hybrid system, is that one must demonstrate the functional significance of the protein-protein interaction that one has discovered" (page 62, col. 1, top of the third full paragraph). Additionally, there is also no evidence of record (*in vitro* or *in vivo*) indicating that the E_o protein of the present invention can disrupt the E1 and E2 heteromeric complex (already formed complex) that is thought to be necessary for HCV virus binding and entry to the cells as taught by Yi et al. and asserted by Applicants.

With respect to the issue on how a simple administration of an effective amount of E_o protein into a subject would result in the disruption of the endogenous E1/E2 heteromeric complex already present in the HCV virus and thereby disrupting HCV virus binding and entry into target cells, Applicants argue that the formation of stable E1-E2 complexes is slow with $t_{1/2}$ about 2 hrs as taught by Cocquerel et al., and therefore an agent (for this instance E_o protein) has sufficient time to interfere in this complex formation. Additionally, Applicants argue that interruption of this complex formation is not necessary for inhibition of binding of E2 to a cell because Applicants' binding data is based on E2 is independent of whether E2 is alone or in complex with E1. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, HCV particles acquire the already formed E1-E2 complexes on their envelopes by budding at internal membranes, most probably in the endoplasmic reticulum where both E1 and E2 are co-expressed, co-localized and interact to form the heterodimeric complexes (see the entire article of Cocquerel et al.). Therefore, it is unclear how the administered E_o protein could interfere in anyway with these functional units that mediate binding and entry of HCV particles into target cells. It is noted that this is not a situation where the newly synthesized E1 and E2 proteins start to be assembled into functional units on the envelope of an HCV particle, and that due to their slow association $t_{1/2}$ (about 2 hrs) for forming a stable E1-E2 complex, the administered E_o protein could interfere and disrupt the formation of the functional E1-E2 complex.

Secondly, Applicants' truncated $E2_{384-661}$ expressed in the yeast two hybrid assay system is not a physiological form of E2 protein that would be present on the surface of

HCV particles because Applicants' truncated E2 protein is fused with the GAL4 DNA binding domain, and that it is not even at least in the non-covalent E1-E2 complex, a functional unit that mediates entry of HCV into target cells (Yi et al., Virology 231:119-129, 1997; Cited by Applicants previously in Exhibit 17). Moreover, apart from the yeast two hybrid assay system, there is no evidence of record indicating that the E_o or E_o1 protein is capable of competing or interfering the binding any functional E2 protein or E1-E2 complex to target cells *in vitro* or *in vivo*, and thereby inhibiting the attachment of HCV particles onto a cell.

Therefore, with the lack of sufficient guidance provided by the present disclosure, particularly in the absence of any reasonable correlated *in vivo* example for the method as claimed, the unpredictability of the physiological art as well as the state of the art on the treatment of HCV in a subject, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Accordingly, amended claims 44-49 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Tiffiany Tabb, whose telephone number is (703) 605-1238.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER